Bevacizumab in Combination with Taxane versus Non-Taxane Containing Regimens for Advanced/Metastatic Nonsquamous Non–Small-Cell Lung Cancer

A Systematic Review

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Background: In preclinical studies, the efficacy of the combination of antiangiogenic agents with chemotherapy seems to be dependent on the specific cytotoxic agent. We conducted a systematic review of the efficacy of bevacizumab in combination with taxane or non-taxane containing regimens for untreated, nonsquamous non–small-cell lung cancer patients.

Methods: An extensive search of published clinical trials was conducted from electronic databases (MEDLINE, EMBASE, and Cochrane) and meeting proceedings using relevant search criteria. Phase 2 and randomized trials reporting on the efficacy of bevacizumab combined with taxane or non-taxane regimens were selected. A systematic analysis of extracted data was performed using Comprehensive Meta-Analysis (Version 2.2) software. Clinical outcome in patients treated with taxane versus non-taxane regimen was compared using point estimates for weighted values of median overall survival, progression-free survival, and response rate.

Results: Twenty-nine studies reported between 2005 and 2015 were eligible. A total of 5890 patients (2767 and 3123 in the taxane and non-taxane groups, respectively) were included. The taxane and non-taxane groups were comparable in patient characteristics: median age, 62.8 versus 61.2 years; males, 57% versus 58%; adenocarcinomas, 83% versus 83%; stage IV, 87% versus 82%; performance status 0/1- 45/55% versus 41/59%, respectively. The weighted median overall survival was 14.4 versus 13.7 months ($p = 0.5$); progression-free survival was 6.93 versus 6.99 months ($p = 0.61$); response rate was 41% versus 39% ($p = 0.65$) for taxane and non-taxane groups.

Conclusions: The outcomes between taxane and non-taxane regimens when given in combination with bevacizumab for patients with nonsquamous non–small-cell lung cancer are comparable.

Key Words: bevacizumab, taxanes, systematic review.

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Tumor growth depends on the presence of adequate blood supply. This is driven by an "angiogenic shift" in the balance of growth factors, favoring proangiogenic growth factors, such as vascular endothelial growth factor (VEGF).[1] Because of the dependence of tumor survival and growth on angiogenesis, blockade of the VEGF pathway has emerged as a rational target for therapeutic intervention. Bevacizumab is a humanized monoclonal antibody that binds VEGF-A and inhibits VEGF receptor (VEGFR) signaling. It is approved for the treatment of a variety of malignancies including first-line treatment of advanced stage nonsquamous non–small-cell lung cancer (NSCLC) in combination with carboplatin and paclitaxel, although it is also used with other chemotherapy doublets in routine clinical practice.

NSCLC remains the most lethal form of cancer, with over 150,000 deaths estimated in 2013 in the United States.[2] In patients with NSCLC, the overexpression of VEGF protein and mRNA levels has been associated with worsened survival.[3,4] In preclinical studies, cytotoxic agents, such as docetaxel, decrease endothelial cell proliferation, thereby increasing the efficacy of VEGFR blockade by bevacizumab.[5] Bevacizumab in combination with platinum-based chemotherapy in chemotherapy naive patients with advanced NSCLC has been shown to increase both objective response rates (ORR) and progression-free survival (PFS) in phase 3 studies.[6–8] The E4599 study demonstrated significantly improved median survival from 10.3 months in the control arm to 12.3 months with the addition of bevacizumab to carboplatin and paclitaxel. A second trial that randomized patients to the regimen of cisplatin and gemcitabine with or without bevacizumab revealed a modest improvement in PFS, which did not translate into survival advantage. Another recent study that compared the

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combination of carboplatin, pemetrexed, and bevacizumab did not demonstrate a survival advantage over carboplatin, paclitaxel, and bevacizumab (POINTBREAK study).[9] This study also included different maintenance strategies between the two arms. The patients on the pemetrexed arm received both pemetrexed and bevacizumab, whereas the control group received bevacizumab monotherapy for maintenance.

The results from recent trials prompted the question of whether the enhancement in efficacy of chemotherapy with bevacizumab may be dependent on specific chemotherapy agents. Indeed, preclinical data indicate that taxanes result in release of endothelial progenitor cells, an effect that has not been observed with gemcitabine.[10] This work provided a potential explanation for the lack of survival benefit with studies that combined bevacizumab with non-taxane chemotherapy agents. To understand this issue better, we performed a systematic review of published trials to compare the efficacy of bevacizumab in combination with taxane containing regimens versus non-taxane containing regimens in front-line setting.

METHODS

Search Strategy

A comprehensive and methodical search of the literature of electronic databases (Medline, Embase, and Cochrane) for studies published between 2005 and 2015 was conducted. Applicable terms, such as "bevacizumab and NSCLC," were used with the filters "clinical trial," "humans," and "all adult: 19+ years" for the MEDLINE searches. Relevant abstracts were searched and retrieved from the conference proceedings of annual meetings of the American Society of Clinical Oncology and from the World Conference on Lung Cancer.

Study Eligibility

The studies were independently reviewed by two of the authors (M.B. and R.P.) for eligibility. Trials using bevacizumab in combination with a taxane or non-taxane regimen in the front-line setting were included in this analysis. Trials were excluded if the taxane or non-taxane containing regimen did not include platinum. Trials in the non-taxane arm were eligible only if they included standard cytotoxic drugs, such as pemetrexed, gemcitabine, vinorelbine, or etoposide in the regimen. Phase 1 trials or trials that enrolled less than 20 patients were excluded from the analysis. Studies were included if at least one of the outcome measures was extractable in an analyzable form. All prospective randomized, nonrandomized, and single arm studies that met the inclusion criteria were identified for the analysis.

Data Extraction and Statistical Analysis

The extracted data included demographics, treatment, and clinical outcomes (ORR, overall survival [OS], PFS, and toxicities). From trials that investigated multiple treatment arms, data were only included from the arms that reported on bevacizumab and platinum with taxane or standard non-taxane drug (three drugs regimen) in each group. The outcome data extracted for each arm were analyzed using random and fixed-effect models and reported as weighted measures. Overall grade 3–5 toxicities and the most common toxicity were extracted for comparisons between the two groups. All analyses were performed using Comprehensive Meta-Analysis software (CMA Version 2.2) and SAS statistical package V9.3 (SAS Institute, Inc., Cary, NC). The comparisons between the two arms were conducted based on weighted estimates. Two-tailed *T*-test with a significance level of 0.05 was used for all comparisons. Heterogeneity among studies was assessed using the I^2 test.[11]

RESULTS

A total of 951 studies were reviewed, and 29 studies published between 2005 and 2015 were included in the final analysis (Fig. 1). Two of the studies included in this analysis reported on both taxane and non-taxane groups.[9,12] With the exception of two trials[13,14] that included docetaxel, all other studies in the taxane arm included paclitaxel in the regimen in combination with cisplatin or carboplatin. All studies in the non-taxane group included pemetrexed or gemcitabine in the regimen, except for one trial that included only vinorelbine[15] in the combination. The phase 4 SAiL study included pemetrexed, gemcitabine, vinorelbine, and etoposide in the platinum doublet regimen.[12] A total of 5890 patients (2767 and 3123 in the taxane and non-taxane groups, respectively) were included. The most common chemotherapy agents used with

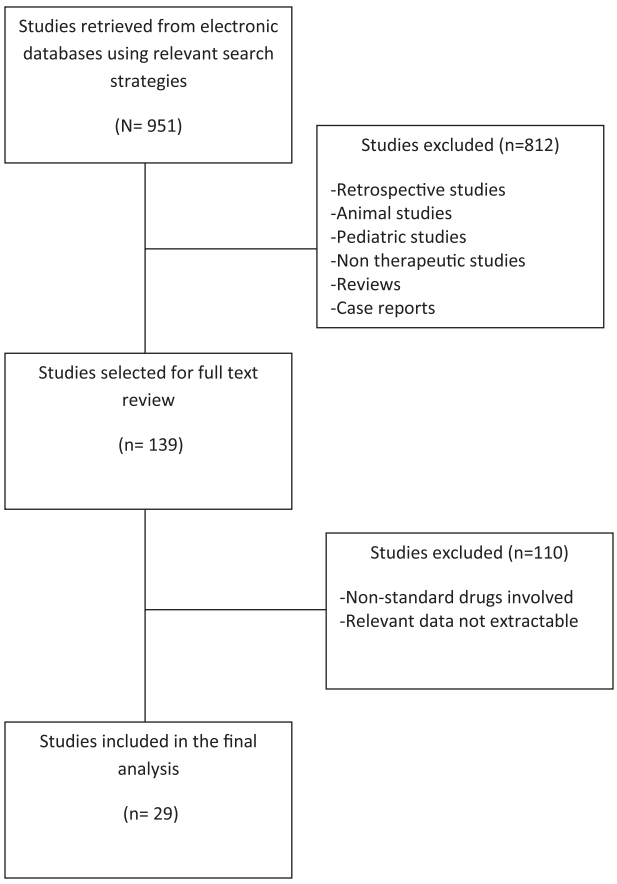

FIGURE 1. CONSORT diagram outlining study selection.

bevacizumab among non-taxane regimens were gemcitabine (51%) and pemetrexed (30%). However, 55% of the patients who were treated with gemcitabine were part of the SAiL study.[12]

The taxane and non-taxane groups were comparable in patient characteristics (Table 1): median age, 62.8 versus 61.2 years; males, 57% versus 58%, adenocarcinomas, 83% versus 83%; stage IV, 87% versus 82%; performance status 0/1- 45/55% versus 41/59%, respectively.

Efficacy

Due to significant heterogeneity among the studies in the taxane and non-taxane arms (I^2 = 81% and 74%, respectively, $p < 0.0001$), a random effect model was employed to estimate the pooled ORRs. The weighted pooled ORR for the taxane arm (N = 1973) was 41% (confidence interval [CI]: 36–47%; Fig. 2), and that for the non-taxane arm (N = 1706) was 39% (CI: 33–44%); $p = 0.65$. The weighted mean of the overall median survival time was estimated and compared from the studies that reported the data; the median survival was 14.4 months with taxanes (N = 2741) and 13.7 months with non-taxanes (N = 3032; $p = 0.5$).

The weighted mean of the PFS time was compared between the two arms from the studies that reported the data; the median PFS was 6.93 months with taxanes (N = 2767) and 6.99 months with non-taxanes (N = 3078; $p = 0.61$).

There were no significant differences in OS and PFS when the taxane group was compared separately with pemetrexed (N = 823; OS: 14.4 versus 13.2 months, $p = 0.50$; PFS: 6.93 versus 6.6 months, $p = 0.40$) and gemcitabine (N = 743; OS: 14.4 versus 13.4 months, $p = 0.66$; PFS: 6.93 versus 6.73 months, $p = 0.59$) based studies. However, the response rate (RR) in the gemcitabine group was lower than that of the taxane group (29% versus 41%, $p = 0.06$) and significantly lower than that of the pemetrexed based group in the non-taxane arm (29% versus 45%, $p = 0.03$). The RR was comparable between taxane and pemetrexed groups (41% versus 45%, $p = 0.5$).

Among studies that reported rates of grade 3–5 toxicities, rates were estimated to be lower in the taxane group than the non-taxane group (59% CI: 51–66% versus 69% CI: 63–75%; $p = 0.10$). Neutropenia was reported as the most common toxicity in the taxane group with a higher proportion than in the non-taxane group (36% CI: 27–46% versus 27% CI: 19–36%; $p = 0.26$). However, the differences were not statistically significant.

In a subset analysis of only phase 2 and 3 studies (excluding the phase 4 SAiL study), OS was similar between taxane (N = 1947) and non-taxane (N = 1615) groups (13.9 versus 13.4 months, $p = 0.83$). Similar analysis of PFS showed no difference between the taxane (N = 1973) and non-taxane (N = 1661) groups (6.3 versus 6.6 months, $p = 0.85$).

DISCUSSION

Following the approval of bevacizumab for the treatment of advanced nonsquamous NSCLC by the FDA in 2006, a number of efforts have been undertaken to optimize utilization of this agent. The search for predictive biomarkers by studying circulating endothelial cells, tumor expression of angiogenic markers, novel imaging methods, etc. has been unsuccessful to date. There is a great interest in understanding the optimal patient population and setting in which bevacizumab should be used in advanced NSCLC.

We sought to understand the role of specific chemotherapy partners in impacting the outcome of bevacizumab-based therapy. In a series of elegant preclinical experiments, Shaked et al.[10] demonstrated that certain chemotherapy drugs, such as taxanes, induce the release of circulating endothelial progenitor cells that are proangiogenic. Pretreatment of mice with antiangiogenic agents abrogated the taxane-induced release of endothelial progenitor cells. This observation was, however, not seen with gemcitabine, another often used cytotoxic agent in NSCLC therapy. Although taxanes including paclitaxel, nab-paclitaxel, and docetaxel are often used for the treatment of advanced NSCLC, pemetrexed, gemcitabine, and vinorelbine are also effective agents that are part of the therapeutic armamentarium. The purpose of our systematic analysis of this issue was to determine whether the therapeutic benefit with bevacizumab is restricted to certain combination partners.

Inclusion of nearly 6000 subjects treated with bevacizumab in this analysis provides for a robust database to inquire about the role of specific chemotherapy agents. The representation of patients treated with taxane and non-taxane regimens was comparable. We found that RR, PFS, and OS were similar for the combination of bevacizumab with taxane and non-taxane regimens. An inherent limitation of such retrospective analyses of published data is the heterogeneity among the studies because of the variability of patient populations included, varying chemotherapy dose and schedules and differences in study designs. Another limitation of this study is that nearly 50% of patients (including 899 patients reported in the phase 4 SAiL study[12]) in the non-taxane arm received bevacizumab in combination with platinum and gemcitabine. Given the recent knowledge regarding the role of histology in sensitivity to various chemotherapy agents, gemcitabine is not the preferred agent for the treatment of nonsquamous histology. On the other hand, pemetrexed, which is efficacious in nonsquamous histology, only constituted 31% of the non-taxane group. In this limited set, we found no difference between efficacy with pemetrexed-based and taxane-based bevacizumab combinations. However, our analyses showed a significantly higher RR with pemetrexed-based studies when compared with gemcitabine-based studies within the non-taxane group (45% versus 29%, $p = 0.03$). Our subgroup analyses without the SAiL study data also demonstrated comparable efficacy between the taxane and non-taxane groups. Our results are aligned with the data from the POINTBREAK study, which was designed to demonstrate an improvement in survival with the carboplatin, pemetrexed, and bevacizumab regimen over the carboplatin, paclitaxel, and bevacizumab regimen. There was no improvement in OS, and the median survival was comparable between the two arms. Although the primary issue in this study was to compare pemetrexed with paclitaxel in nonsquamous histology, it can also be gleaned that the outcomes with the addition of bevacizumab were not influenced by one chemotherapy or the other.

TABLE 1. Study Characteristics and Summary of Findings

Study	Funding Source and Design	Therapy (with B)[a]	N	Demographics					Outcomes		
				Median Age	Gender Male (%)	PS-0 (%)	AC (%)	Stage IV (%)	OS (mo)	PFS (mo)	ORR (%)
Taxane arm											
Sandler et al.[6]	Public, phase 3, randomized	Pac + Cb	417		50	40	88	74	12.3	6.2	32
Reynolds et al.[16]	Private, phase 2	Pac + Cb	48	67	46	54	90	100	16.8	9.8	31
Socinski et al.[17]	Private, phase 2, randomized	Pac + Cb	26	66	54	38	85	81		4.5	19
William et al.[13]	Private, phase 2	Doc + Cb	40	63	45	28	63	95	16.5	7.9	53
Niho et al.[18]	Private, phase 2, randomized	Pac + Cb	121	61	64	51	92	69	22.8	6.9	59
Soria et al.[19]	Private, phase 2, randomized	Pac + Cb	44	58	52	39	73	100	15.1	7.3	50
Blumenschein et al.[20]	Private, phase 2, randomized	Pac + Cb	63	64	56	52	86	83	14	8.3	37
Crinò et al.[12]	Private, phase 4		794						15.5	8.3	
Kentepozidis et al.[14]	Private, phase 2	Doc + Cis	48	61	77	46	83	79	13.3	4.4	33
Besse et al.[21]	Private, phase 2	Pac + Cb	67	61	69	55	88	100	16	6.7	63
Tamiya et al.[22]	NR, phase 2	Pac + Cb	23	68	78	9	100		10.9	6.7	61
Galetta et al.[23]	Private, phase 3, randomized	Pac + Cb	58	62.5	78	79	97	93	14.4	8.3	52
Patel et al.[9]	Private, phase 3, randomized	Pac + Cb	467	64.9	53	44	78	90	13.4	5.6	33
Zinner et al.[24]	Private, phase 3, randomized	Pac + Cb	179	66	58	47	77	100	11.7	5.5	27
Twelves et al.[25]	Private, phase 2, randomized	Pac + Cb	60		62	27	80	92	13.3	6.1	43
Massuti et al.[26]	Public, observational	Pac + Cb	200	61	67		88	98	14.57	6.91	36
Dingemans et al.[27]	Public, phase 2, randomized	Pac + Cb	112	62	50		85		11.6	6.8	45
Non-taxane arm											
Stevenson et al.[28]	Private, phase 2	Pem + Cb	43	65.3	47	84	77	86	17.1	7.1	44
Spigel et al.[29]	Private, phase 2, randomized	Pem + Cb	55	77	47	38	80	85	14.8	10.2	35
Casey et al.[30]	Private, phase 2, randomized	Pem + Cb	20	61.2	50	55		85	7.6	4.3	30
Clément-Duchêne et al.[31]	Public, phase 2	Gem + Cb	47	59	49	6	64	83	12.8	8.7	15
Patel et al.[32]	Private, phase 2	Pem + Cb	50	63.5	44	32	94	82	14.1	7.8	54
Reck et al.[7]	Private, phase 3, randomized	Gem + Cis	345	57	65	40	85	77	13.6	6.7	34
			351	57	62				13.4	6.5	30
Crinò et al.[12]	Private, phase 4	Pem/Gem/Eto/ Vin + Cis/Cb	1417						14.1	7.4	
Lopez-Vivanco 2012[33]	Private, phase 2	Pem + Cis	21	58	81	5	95			6	33
Guarino et al.[34]	NR, phase 2	Pem + Cb	50	64	52				11.2	5.5	52
Patel et al.[9]	Private, phase 3, randomized	Pem + Cb	472	64.6	53	44	80	90	12.6	6	34
Schuette et al.[35]	Phase 3, randomized	Pem + Cb	133	72	65		76		15.2	6.8	44
Murakami et al.[36]	NR, phase 2	Pem + Cis	25	62	76			84		10.3	64
Yanagitani et al.[37]	NR, phase 2	Pem + Cis	45	61	44	67	100				60
Leon et al.[15]	Private, phase 2	Vin + Cis	49	59	73	33	82	78	14.7	6	27

[a]In the trials with multiple treatment arms, only the arms reporting on (B + platinum) with taxane or non-taxane were included in the analysis.

B, bevacizumab; Pem, pemetrexed; Cb, carboplatin; Cis, cisplatin, Doc, docetaxel; Pac, paclitaxel; Gem, gemcitabine; Vin, vinorelbine; Eto, etoposide; ORR, objective response rate; NR, not reported; PS, performance status; AC, adenocarcinoma.

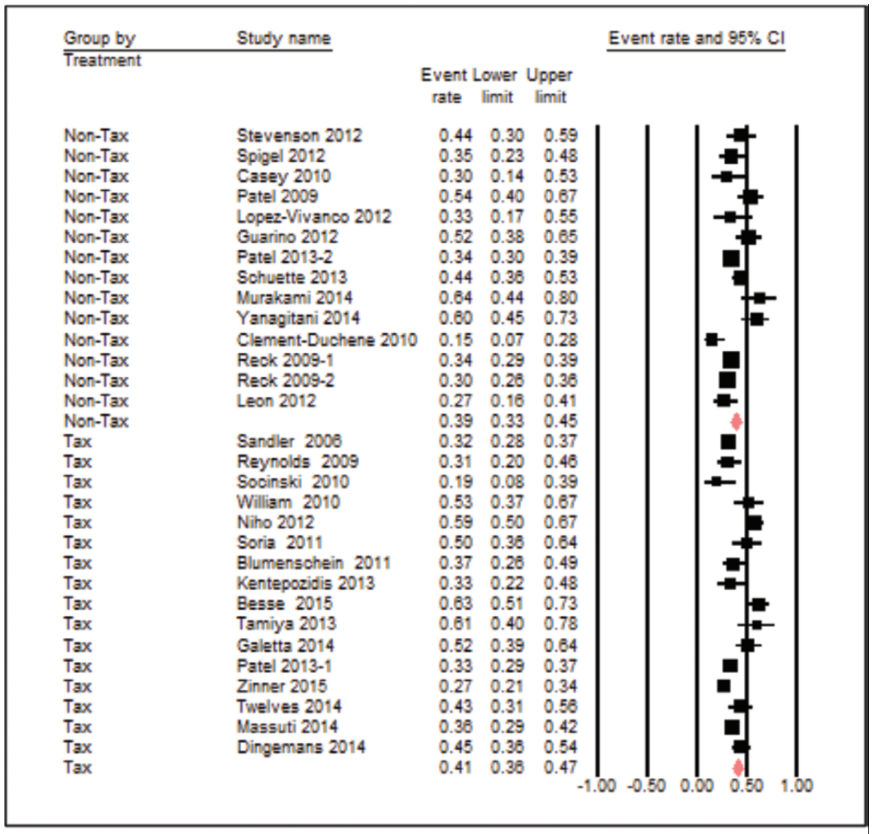

FIGURE 2. Response rate (RR), non-taxane versus taxane arm, 39% versus 41%.

From this analysis, we conclude that the efficacy of bevacizumab appears to be comparable when used with either a taxane-based or a non-taxane-based combination regimen in advanced nonsquamous NSCLC. The most important fact remains that for agents that add a relatively modest efficacy to existing therapies, the absence of a biomarker to identify sensitive populations is a major hurdle for optimal utilization.

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